ACTIVE PHARMACEUTICAL INGREDIENTS COMMITTEE

A SECTOR GROUP OF CEFIC

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852
USA

Courtesy copy:
Dr. Roger Williams, Director
FDA/CDER
Office of Pharmaceutical Science
6027 Woodmont Office Complex 2
Rockville, MD 20852
USA

Docket No. 99D-0529

6 August 1999

Dear Sirs,

Please find hereunder the comments from:

CEFIC/APIC (European Chemical Industry Council/Active Pharmaceutical Ingredients Committee)
Avenue E. van Nieuwenhuyse 4, bte 2
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Belgium
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on FDA's Draft "Guidance for Industry: Changes to an Approved NDA or ANDA" (June 1999).

CEFIC is the organization representing national federations, companies and more than 100 affiliated associations and sector groups, located in Europe. All together CEFIC represents directly or indirectly more than 40,000 large, medium and small chemical companies in Europe, which employ about 2 million people and account for more than 30% of the world's chemical production.
APIC is one of CEFIC's sector groups, comprising producers of active pharmaceutical ingredients (APIs) and intermediates in Europe. The major part of the total volume of APIs and intermediates imported into the USA originates from

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Europe. For this reason, CEFIC/APIC considers itself to be a very important stakeholder in new FDA Guidances related to APIs and intermediates.
We, therefore, highly appreciate this opportunity for submitting our European APIs- and intermediates manufacturing members' comments on the above mentioned Draft Guidance, which in part deals with changes relating to the manufacture of our products.

The API related aspects of the Draft Guidance on "Changes to an Approved NDA or ANDA" are closely linked to those which were included in FDA's recently issued Draft "BACPAC I" Guidance (as well as to the yet to be issued Draft "BACPAC II" Guidance). Therefore, the majority of CEFIC/APIC comments on the Draft "BACPAC I" Guidance, which we recently submitted to the FDA, are of direct relevance to this newly issued Draft Guidance as well.
For this reason, we enclose a copy of our previously submitted comments on the "BACPAC I" Draft Guidance for your reference, instead of repeating them here.

We find it important to emphasize that our previously submitted comments on the BACPAC I Draft, which were designated as Type * * * and Type * * comments, were not intended to plead for somewhat more flexibility within the proposed procedures and requirements for getting post-approval changes authorized. These comments actually originated from the much more serious concern that the proposed procedures and requirements would result in the impossibility for dedicated API- and intermediates manufacturers, who are holders of DMFs, to get (often unavoidable) post-approval changes authorized at all.
We refer to page 3 of the enclosure for an explanation on the reasons for this, obviously highly undesirable, result of the proposed BACPAC I Guidance. Suggestions from CEFIC/APIC for resolving this problem are also described on that same page.

Since the Draft Guidance "Changes to an Approved NDA or ANDA" includes proposals for API-related post-approval changes procedures and requirements which are very similar to those which were included in the BACPAC I Draft, we would like to request FDA to take our comments and suggestions once more into serious consideration, now with regards to this new Draft Guidance.
The contents of the new Draft Guidance indicates that the comments received by FDA from industry on the BACPAC I Draft have not yet been taken into account during its drafting.

Since the new Draft Guidance also covers the scope of the yet to be issued BACPAC II Draft, we would like to refer again to the suggestions we have included on page 3 of our previously submitted comments. These suggestions cover the entire scope of BACPAC I plus II. They are intended to resolve the entire problem of post-approval change authorization obstructions for DMF holders, whether involved in API- or in intermediate manufacture.

Because CEFIC/APIC regards the above mentioned procedural problems for DMF holders of a paramount importance, which supersedes all other possible needs to fine-tune the Draft, we have decided to refrain from submitting any additional, more detailed comments on the contents of the Draft Guidance.

As stated in our previous comments, CEFIC/APIC does not believe that it is FDA's intention to fully obstruct the implementation of beneficial post-approval changes to bulk pharmaceutical manufacture, because of inadequacies within the available filing mechanism procedures *only*.

CEFIC acknowledges the need for stringent change control regulations to ensure all appropriate measures are taken to safeguard public health. Nevertheless, the current regulations only apply to changes to approved NDAs and ANDAs, which entails that companies importing into the US and selling only to OTC producers are unaffected by these regulations. Over a thousand tons of APIs for the OTC market are imported every year into the US, often without verification of cGMP compliance and where unannounced process changes or changes relating to the origin of supplies are possible.

These companies are subjected to the cGMP change control regulations, however, without verification as no pre-approval and hence, no-follow-up audits are generally involved.

A dramatic example (37 deaths and 1500 permanent disabilities) that readily available molecules can become life-threatening is L-tryptophane, a nutritional supplement banned by the FDA in November 1990. Initially genetic engineering was blamed, but later, changes in the purification techniques appeared to be the causative factor.

This is a clear example where differences in regulations between OTC and prescription drugs is unjustified. No such difference exists in the European Union where the variations regulations apply to all drugs substances, regardless of their prescription status.

CEFIC/APIC would once more like to express its strong commitment to support the FDA in the development of realistic and workable post-approval change Guidance in the area of pharmaceutical bulk manufacture.

Our organization is fully prepared and willing to provide further input and clarification, whenever required.

Sincerely yours,

Chris Oldenhof, Ph.D.
Vice-President
CEFIC/APIC

Loic Le Doré,
APIC Secretary

- Enclosure